

Table The synthesis of some β -hydroxynitriles, -ketones, -esters and -carbonamides via the addition of α -functionally substituted organotins to aldehydes and ketones

Reactants	Addition product	β -Hydroxy derivative
$Bu_3SnCH_2CN + C_6F_5CHO$	$Bu_3SnOCH(C_6F_5)CH_2CN$	$HOCH(C_6F_5)CH_2CN$
$Et_3SnCH_2COCH_3 + PhCHO$	$Et_3SnOCPhCH_2COMe$	$HOCHPhCH_2COMe$
$Et_3SnCH_2COCH_3 + o-ClC_6H_4CHO$	$Et_3SnOCH(C_6H_4Cl-o)CH_2COMe$	$HOCH(C_6H_4Cl-o)CH_2COMe$
$Et_3SnCH_2COCH_3 + m-NO_2C_6H_4CHO$	$Et_3SnOCH(C_6H_4NO_2-m)CH_2COMe$	$HOCH(C_6H_4NO_2-m)CH_2COMe$
$Et_3SnCH_2COCH_3 + furfural$	$Et_3SnOCH(C_4H_3O)CH_2COMe$	$HOCH(C_4H_3O)CH_2COMe$
$Et_3SnCH_2COCH_3 + PrCHO$	$Et_3SnOCHPrCH_2COMe$	$HOCHPrCH_2COMe$
$Et_3SnCH_2COCH_3 + PhCH=CHCHO$	$Et_3SnOCH(CH=CHPh)CH_2COMe$	$HOCH(CH=CHPh)CH_2COMe$
$Et_3SnCH_2COCH_3 + ClCH_2COCH_2Cl$	$Et_3SnOC(CH_2Cl)_2CH_2COMe$	$HOC(CH_2Cl)_2CH_2COMe$
$Et_3SnCH_2COCH_3 + \text{cyclohexanone}$		
$Et_3SnCH_2COCH_3 + 2-naphthalenone$		
$Et_3SnCH_2CO_2Et + CCl_3CHO$	$Et_3SnOCH(CCl_3)CH_2CO_2Et$	$HOCH(CCl_3)CH_2CO_2Et$
$Et_2Sn(CH_2CO_2Me)_2 + CCl_3CHO$	$Et_2Sn[OCH(CCl_3)CH_2CO_2Me]_2$	$HOCH(CCl_3)CH_2CO_2Me$
$Et_2Sn(CH_2CO_2Me)_2 + PhCHO$	$Et_2Sn(OCHPhCH_2CO_2Me)_2$	$HOCHPhCH_2CO_2Me$
$Et_2Sn(CH_2CO_2Me)_2 + furfural$	$Et_2Sn[OCH(C_4H_3O)CH_2CO_2Me]_2$	$HOCH(C_4H_3O)CH_2CO_2Me$
$Et_2Sn(CH_2CO_2Me)_2 + CF_3COPh$	$Et_2Sn[OC(CF_3)PhCH_2CO_2Me]_2$	$HOC(CF_3)PhCH_2CO_2Me$
$Et_3SnCH_2CONEt_2 + C_6F_5CHO$	$Et_3SnOCH(C_6F_5)CH_2CONEt_2$	$HOCH(C_6F_5)CH_2CONEt_2$
$Et_3SnCH_2CONEt_2 + PhCHO$	$Et_3SnOCHPhCH_2CONEt_2$	$HOCHPhCH_2CONEt_2$
$Et_3SnCH_2CONEt_2 + CCl_3CHO$	$Et_3SnOCH(CCl_3)CH_2CONEt_2$	$HOCH(CCl_3)CH_2CONEt_2$

substituents attached to the carbonyl group. Examples of easily reacting aldehydes are chloral and pentafluorobenzaldehyde. Lewis acids, e.g. zinc chloride, may be used as catalysts.

The hydrolysis step is preferably carried out with oxalic acid, because the organotin oxalates formed are little soluble in organic solvents and therefore easily separated. Also with oxalic acid there is no risk of dehydration of the hydroxy derivative as may occur with hydrochloric acid.

The reaction described above is closely related to the so-called Reformatsky reaction. Its scope is however, wider and it also has the advantage over the Reformatsky reaction of proceeding with much higher yields. It is hoped that this reaction will lend itself to the synthesis of natural products, e.g. steroids, or the transformation of such products in potentially useful derivatives.

With a view to application on an industrial scale the results obtained have been incorporated into two patent applications.^{12,13}

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UKAEA win reactor contract

The United Kingdom Atomic Energy Authority have won a contract valued at about £330,000 to design and supply a nuclear reactor for a new type of nuclear power station being built in West Germany.

The function of the reactor is to make possible the correct fuel reloading of the 300MW(e) thorium high temperature 'pebble-bed' reactor (THTR) now under construction by Hochtemperatur Reaktorbau GmbH at Schmehausen near Dortmund. The reactor, known as the Solid Moderated Reactor (SMR), will be designed, built and calibrated at the Authority's Reactor Group Establishment at Winfrith, Dorset, where tests on 'Hector', one of the research reactors located there,

have demonstrated the feasibility of the system.

The THTR is the first commercial 'pebble-bed' type of reactor to be built. Its core consists of a large tank filled with graphite spheres containing inserts of highly enriched uranium fuel and thorium breeder material. The graphite acts as a moderator and the thorium, under neutron bombardment, converts to the artificial fissile isotope ^{233}U . Spheres are continuously fed to the top of the core tank, with a corresponding rate of removal of spheres from the base, after which they are recycled until they have reached the maximum specified burn-up.

The reactivity of spheres emerging from

the base of the THTR is measured in the SMR, which consists of an 80in cube of graphite through which passes a zircaloy tube at an inclination of five degrees to the horizontal. After removal from the THTR core each sphere passes down the tube through the centre of the SMR core, in doing so affecting the power level of the SMR to an extent depending on the reactivity and hence the burn-up of the fuel in the sphere. This is measured and transmitted to a computer which determines the destination of each sphere.

The SMR will be designed, erected and calibrated at Winfrith before delivery, re-erected at Schmehausen, and handed over in mid 1974.

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Patterns of innovation

Part II – The anaesthetic halothane*

F R Bradbury, M C McCarthy and C W Suckling

In the previous article two models of innovation were discussed, and the implications of these theories for practising industrial research scientists examined. In this and one subsequent article we describe two major innovations in the chemical industry, and use the model of innovation based on the definition of an innovative chain to structure these case studies.

The anaesthetic halothane

Halothane is the generic name for the anaesthetic whose proprietary name is 'Fluothane'. It is now widely used for a great variety of surgical operations. Recent reports have commented on its advantages. One remarks that: 'it has exceptionally valuable properties, for it is potent, non-irritant to the respiratory tract, and can be used in the closed-circuit apparatus in the presence of warm soda-lime'; a second claimed that: '... its introduction represents one of the most important advances in anaesthesia of the century'.¹ It now is estimated to be used in about 70 per cent of all general surgical anaesthesia administered in the UK. Yet even a product which, in the course of time, has gained so widespread an acceptance had a difficult birth and an insecure childhood. Analysis of halothane's discovery and introduction to the market shows there to have been many barriers to be surmounted, not only in initiating successful research, but also in ensuring the compound's development. Successful innovation depended on several groups of people, each possessing different criteria and motivation. Differences between these groups accounted for many of the difficulties in halothane's development. Analysis of the innovation must therefore be concerned not only – or even mainly – with its origins, but also and principally with the elaboration of the original invention into the innovation.

Before halothane's discovery, the anaesthetist had several inhalant anaesthetics from which to choose as well as

intravenous anaesthetics. The inhalant anaesthetics included chloroform, nitrous oxide, cyclopropane, and ether. All, however, suffered from at least one serious defect – explosiveness, toxicity, unfortunate side-effects, or inadequate potency. Ether, the most commonly used inhalant anaesthetic, caused a considerable explosion hazard; chloroform carried with it the risk of severe damage to vital organs, and had been characterised as being 'almost universally recognised as too poisonous for the production of surgical anaesthesia in human beings'.² Yet despite the acknowledged deficiencies in all inhalant anaesthetics, little advance had been made in introducing new inhalant agents. Rather the advances in anaesthesia had been the development of intravenous anaesthetics, particularly the barbiturates and associated techniques.

The search for a new anaesthetic

Before the search that was to prove successful, at least two attempts had been made to investigate fluorine compounds as potential anaesthetics. In 1932 Booth and Bixby investigated two fluorine analogues of chloroform, and in 1946 Robbins reported trials of 42 fluoroalkanes as anaesthetics. Neither resulted in the identification of a suitable compound, although Robbins considered four compounds worthy of further test.³

The search that led to the successful innovation started in ignorance of these approaches. In 1950, Dr J. Ferguson, research director of the General Chemicals Division of ICI, now part of Mond Division, embarked on a review of the fluorine technology that had been acquired as a necessary adjunct to the manufacture of uranium hexafluorides and fluorolubes. He concluded that the outstanding property of fluorine compounds was the inertness possessed by some; among the uses to which this could be put were anaesthetics. As a result of his review, Ferguson asked Dr C. W. Suckling to start work in September 1950 on fluorine research to produce a new anaesthetic. Suckling soon contacted the

part of ICI with most experience in pharmaceutical matters, the Medicinals Section of Dyestuffs Division, the forerunner of Pharmaceuticals Division, and in February 1951 the two organisations submitted a sanction for a research programme by which compounds would be synthesised at Widnes by Suckling, and tested by an ICI anaesthetist and pharmacologist, Dr J. Raventós, at Manchester.

The initial task was to define their target. The approach of defining a target was a novel step in the research environment of 1951, and it was not an easy one. The properties of a good anaesthetic are for the most part defined – as is anaesthesia itself – in relation to the effects observed on an anaesthetised patient, rather than being defined in relation to the compounds used to obtain anaesthesia. The requirements were multiple. The accepted definition of the ideal inhalant anaesthetic specified four people who must be satisfied. The patient required a gas producing rapid and pleasant induction, was non-irritating and did not cause discomfort; the surgeon desired a non-explosive gas which did not inhibit his surgical techniques in any way; the anaesthetist required a compound with good margin of safety, that was excreted from the body unchanged, enabled him to have moment to moment control of the depth of anaesthesia, was highly potent, and produced no functional or organic damage; the manufacturer, it was claimed, wanted a chemical simply and inexpensively made, easy to purify, transport and store.⁴ (Margin of safety may be defined as the ratio between the concentration required to produce anaesthesia in a proportion (normally 50 per cent) of the test animals to which it was administered (the AD₅₀ concentration), and the concentration required to produce death in the same proportion of test animals (LD₅₀). Thus

the safety margin or therapeutic index is calculated as $\frac{LD_{50}}{AD_{50}}$.)

Confronted with such a list of requirements, the researchers had to decide which might be related, via scientific theory or empirical observation, to properties defined in terms of the compounds to be synthesised. Some properties were unpredictable: muscular relaxation and the absence of interference with cardiac regularity are two important examples. The problem was to abstract from the lengthy and formidable list of properties required in an adequate anaesthetic those properties which might be related to the physical and chemical properties of the compound in question. The number of fluorine containing compounds that could be synthesised was very large: what chemical criteria were to be adopted to define those which should first be made? The properties that were initially selected to define the target were:

1 volatility, for simple vaporisation, which could be related to boiling point

2 non-flammability, which could be aimed at by ensuring that few hydrogen atoms were present in the molecule

3 stability over soda-lime, which could be aimed at by ensuring that the compound would not readily eliminate HCl or HBr

4 high potency, so that the anaesthetic might be administered with large oxygen concentrations. In translating this into chemical terms, Suckling was guided by the treatment of narcosis suggested by Ferguson. By narcosis is meant a reversible inhibition of a biological function. This theory had postulated that a good measure of the narcotic power of a compound was its thermodynamic, rather than its ordinary, concentration. Whereas there were very large differences in the volume concentration required to produce

anaesthesia between different compounds (95 per cent for nitrous oxide, 0·5 per cent for chloroform), thermodynamic concentrations – for which relative saturation may be taken as a reasonable approximation – ranged less widely: both nitrous oxide and chloroform produced anaesthesia at a relative saturation of 0·01. By using this treatment of narcosis, it was possible to relate anaesthetic potency to a physical chemical property of compounds.

The definition of the target described above was probably the most important single step in ensuring halothane's success. By the careful analysis of the properties required of an anaesthetic, and still more by the decision to use four criteria related to physical and organic chemistry, the researchers formed a bridge between the demands of a market and the power of relevant science. It is interesting to observe that Ferguson's treatment of narcosis, a corner stone of the bridge – although quite independently formulated by him – was not new: Snow, writing in 1859, had stated a similar proposition: observing anaesthesia produced by three drugs, he noted that 'We find that the quantity of each substance in the blood in corresponding degrees of narcotism, bears a certain proportion to what the blood would dissolve – a proportion that is almost exactly the same for all of them'.⁵ It fell to Suckling to recognise the significance of this treatment of narcosis in a way that had not previously been seen, even by Ferguson.

The criteria adopted for the first screen were necessary, but in no way sufficient. Success according to the chemical screen may be equated with an inert compound readily volatilised, which was predicted to possess narcotising power. To be acceptable as an anaesthetic, more complex pharmacological targets, not translatable – then or now – into chemical or physical properties, had to be attained. The testing of compounds against these targets was the responsibility of Raventós. His achievement was to define accurate trials to test the small quantities of fluoroalkanes synthesised, so that they were not wasted, and so that the maximum amount of information was obtained from tests. Whereas the chemist based his syntheses on four criteria, the pharmacologist examined seven desirable properties. These were:

non-flammability

high potency

high therapeutic index

freedom from liability to damage a vital organ

rapid and quiet induction and recovery

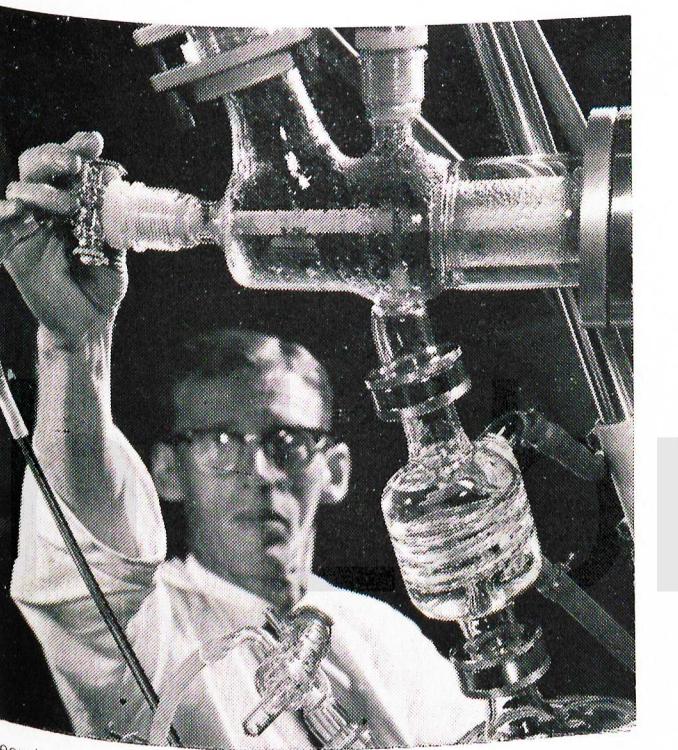
freedom from severe cardiovascular effects.

Success was decided by the results of three stages of tests, in which compounds were actually administered as anaesthetics for progressively mice, rabbits, and cats and dogs. The tissues of various animals anaesthetised with compounds were subjected to pathological and histological studies.

It is interesting to contrast the types of screens designed by Raventós and Suckling, who together had defined their common research target. Whereas the chemist's screen was based on a theoretical explanation of narcosis, the pharmacologist's was much more empirical – indeed, Raventós was initially sceptical of Ferguson's treatment that was so fundamental to Suckling's screen. The two screens, different in nature and in form, were mutually beneficial: the former enabled scientific advances in chemistry to be harnessed to a perceived need, while the latter ensured that the theoretical analysis was justified, and that the full pattern of complex properties needed was investigated. The information needed

at each stage, the language adopted to convey this information and the criteria used to gain the information, had each changed. The overall research target remained constant.

The success of the two screens, the first abstracted, the second more complete, may be seen in two ways. First, between one-half and two-thirds of all compounds synthesised passed the first stage of the pharmacological screen, thus demonstrating the success with which initial criteria had been defined. Second, the anaesthetic that eventually emerged from the combined screens satisfied criteria which would have caused all existing inhalant anaesthetics to be rejected: ether and cyclopropane would have failed as inflammable, chloroform because of damage to vital organs.⁶ The compound identified by the screens was consequently believed by the researchers to be superior to any existing inhalant anaesthetic. This compound – CF₃CHClBr, later known as halothane – was in fact the sixth compound synthesised, and was prepared in January 1953. Clinical trials started in January 1956.



Research on anaesthetics

The successful synthesis owed much to developments that had recently been made in analytic techniques. Previous work on fluorine compounds had been complicated by doubts over the purity of compounds. The advent of gas chromatography enabled those responsible for synthesising candidate anaesthetics to be confident of achieving a high standard of purity; enabled impurities to be identified; and facilitated the scale-up of production techniques.

Clinical trials

The anaesthetist invited to conduct clinical trials was Dr M. Johnstone, of the Crumpsall Hospital, Manchester. Before starting clinical trials, Johnstone scrutinised Raventós' results and observed him anaesthetise various animals. The decision Dr Johnstone had to make, as told to Suckling, was whether the new compound showed promise of giving sufficient benefit to his patient to justify the inevitable uncertainty accompanying the introduction of a new drug. In the light of the evidence put before him, and of his own observations, he answered in the affirmative.

Clinical trials, which started on 20 January 1956, at first

proceeded slowly: by 26 January Johnstone had used halothane in some 23 cases; by 3 February, in some 70 cases, and by 21 February in 120 cases. Throughout, Johnstone showed caution in his use of halothane: for example, he opposed the introduction of 0·01 per cent w/w thymol as a stabiliser until it had been demonstrated that this did not cause respiratory irritation. However, Johnstone's great care not to risk his patients' health was accompanied by an active desire to improve their treatment, and his caution in using halothane was soon allied with a recognition of its qualities. After one month's trial, he reported in conversation that he was confident that halothane had an important place in the theatre. He was particularly impressed by absence of shock syndrome in the patients anaesthetised with halothane; on the table their skin was warm and pink, indicating good circulation; they recovered quickly from anaesthesia, and suffered less post-operative discomfort ascribable to the anaesthesia than was normal.

At the same time that Johnstone was invited to test halothane clinically, the compound was submitted to a Medical Research Council Committee. This committee had been established in 1955 to investigate new non-explosive anaesthetics, and its Chairman, Professor J. H. Burn, had performed some of the pharmacological testing of halothane. It seemed opportune for this committee to investigate halothane's qualities further, and clinical trials were made by some committee members contemporaneously with those conducted by Johnstone.

Barriers to diffusion

At the point when Johnstone reported favourably on clinical trials, the candidate anaesthetic had passed the successive screens established within the research and development stage. Yet to prove useful to the medical profession, and to emerge as a successful commercial venture halothane had still to find acceptance. The internal screens of the R and D departments had been passed; the external barriers to acceptance remained. Anaesthetists had to be persuaded that the compound offered real advantages to their patients; they had to be convinced that it was worth experimenting with it; and that they should continue to use it. In considering the spread of a new product among its users, it is helpful to examine five characteristics of the product suggested by Rogers.⁷ These are:

- 1 The relative advantage of the innovation, and how this is perceived.
- 2 The compatibility of the new idea with existing values.
- 3 The complexity of the new idea, and the need for new adjustments in order to accept it.
- 4 The divisibility of the innovation, that is the ease with which a potential user can experiment before completely adopting it.
- 5 The communicability, or the ease with which advantages possessed by the new idea may be communicated to others.

Relative advantage

The advantages sought by Suckling and Raventós – in addition to the obvious biological requirements – included high potency, easy vaporisation, non-flammability, and the possibility of rapid control of the depth of anaesthesia by the anaesthetist. The main advantages noted by Johnstone were 'the complete absence of the shock syndrome', 'smooth and rapidly reversible anaesthesia', and 'a complete absence of nausea during recovery in over 90 per cent of the patients'.⁸

Of these advantages, there is little doubt which was most important in attracting anaesthetists' attention. Early papers reporting on trials on halothane are dominated by references to its non-explosive nature. An early (and unfavourable) review of clinical trials began: 'our interest in "Fluothane" was first aroused on account of its non-combustibility',⁹ and the authors were undoubtedly speaking for many on this point. It is somewhat ironic therefore that the explosion danger that was avoided when halothane was used, although foremost in the minds of anaesthetists, was probably greatly overemphasised. A 1956 analysis of the incidence of explosions during anaesthesia showed that each year some 0.86 million cases had involved explosive anaesthetics, yet only some five explosions were recorded each year; in the years 1947-54, three people had died as a result of explosions connected with the anaesthetic employed in an operation.¹⁰ The incidence of this danger was small in comparison with some of the enormity of any accidents were such that an anaesthetic which avoided the danger attracted attention.

The danger may have been overestimated, but the inconvenience associated with using explosive anaesthetics was considerable. Verbal reports from anaesthetists suggested that despite low frequency of injury to patients minor but alarming explosions occurred sufficiently often to maintain anxiety as to the use of explosive gases. The precautions necessary included the provision of operating theatres designed to avoid static build-up, and of antistatic clothing; non-sparking equipment had to be used; and cautery was impossible. It was interesting to note that the introduction of halothane has not led – as was originally believed likely – to the total exclusion of explosive anaesthetics. The cost of

Although attention was attracted to halothane because it was non-explosive, this was not the feature which influenced anaesthetists to continue using it. Rather early reports stress the benefits of reduced shock and nausea, suppressed secretion, easy induction and prompt recovery of consciousness. It may fairly be claimed that halothane's non-explosiveness persuaded anaesthetists to try it, but its other qualities made them continue to use it.

Compatibility

To those responsible for its introduction, who were intimately acquainted with its properties, halothane was regarded as a drug totally different from all other anaesthetics, and as the product of research that had utilised the best techniques of whom halothane was introduced regarded it as a throwback to an earlier and discredited tradition in anaesthesiology, and rejected it as such.

To account for this contrast it is necessary to examine the reasoning which led to the initial hostility with which halothane was greeted, at least by some anaesthetists. The basis for their attitude may be explained by the analogy drawn between halothane and chloroform, both of which were chlorinated hydrocarbons, and both non-explosive and highly potent inhalant anaesthetics. Though one of the first features of halothane anaesthesia to strike Johnstone was the absence of the shock syndrome – which was frequent under prolonged chloroform anaesthesia – it was claimed that certain responses of the anaesthetised patient to halothane – some aspects of induction, circulatory and cardiac reactions – were comparable to those occurring when chloroform was

used. It is therefore not surprising that anaesthetists who tried to reduce the complex and unique pattern of end effects produced by halothane to a simpler form used chloroform as their analogy – and chloroform had undeniably dangerous side effects.

The results of this comparison were considerable. First, it suggested that halothane represented a departure from the current line of advance made in anaesthesiology. In the decade before halothane's introduction, the practice of anaesthesia had moved from reliance on an inhalant to do all that was necessary to the use of a carefully formulated cocktail – each component of which performed its own particular pharmacological function. There can be no doubt that this was a most important advance. The advent of halothane, which could be used – like chloroform – for inducing and maintaining anaesthesia, seemed to some anaesthetists to be a retrograde step. The practical implications of this perceptual barrier to halothane's use were great. Chloroform, for example, was recognised as causing extensive liver damage. The comparison drawn between chloroform and halothane made anaesthetists remarkably conscious of any occurrences of jaundice in patients previously anaesthetised with halothane, so that some claimed that this danger negated halothane's advantages, and argued against its use. Subsequent study demonstrated that the incidence of jaundice in patients anaesthetised with halothane was less than the incidence among all patients after anaesthesia; and that it was very much less than that associated with patients after chloroform anaesthesia.¹¹ The alarm with which reports of liver damage following halothane anaesthesia were greeted owed much to the comparison drawn between halothane and chloroform.

There was an even more practical result of treating chloroform and halothane as close analogues, that can be summarised by saying that when halothane was treated as chloroform it behaved as chloroform. By this we mean that when halothane was administered without special techniques – without, for example, special volatilising equipment or special anaesthetic practices developed for halothane – it was indistinguishable from chloroform. A 'blind' study, in which the anaesthetist did not know which agent he administered, concluded that it was not possible to distinguish between halothane and chloroform: '... it was found it was not possible to identify the agent solely by means of its clinical effect ... We believe halothane bears a strong clinical resemblance to chloroform'.¹² The paradigm – the belief that halothane was comparable to, and hence should be treated like, chloroform – was self-justifying, in that when the two were treated in ways that had been developed for chloroform, halothane was constrained to behave in some respects like chloroform. Only when halothane was employed using techniques specially developed for it did its advantages emerge fully. The paradigm thus carried with it a series of practical implications. It was argued that halothane, being compared with chloroform, should be tested on equipment and using techniques, designed for chloroform. Halothane's success demanded the design of new, more appropriate tests, and could be achieved only by escaping from the comparison with chloroform.

Complexity

Just as halothane as a concept was one difficult for some anaesthetists to accept, so too in practice the new anaesthetic presented some problems of adjustment. Two problems were pressing – controlling the concentration of halothane ad-

ministered, and the need to use closed-circuit apparatus. The first problem was a direct consequence – not entirely predicted – of achieving the target of an anaesthetic of high potency. Whereas ether was administered in over ten per cent concentration, halothane was being used in the range one to four per cent. Since only small concentrations of halothane were required, small absolute changes in the concentration delivered to the patient had more effect than the same absolute increase in the concentration of ether or chloroform: to move from three to six per cent of halothane was more hazardous than to move from ten to thirteen per cent of ether. To use halothane safely and reliably, it was necessary to use a volatilising apparatus more accurately calibrated than those hitherto available. Halothane's success therefore depended in part on the development of vapourising equipment of new complexity and accuracy, and on the willingness of anaesthetists to acquire and use these new machines.

A significant contribution was the speed with which manufacturers of anaesthetic equipment responded to the challenge. Halothane required not only vapourisers of new precision, but also that these should not be affected by prolonged exposure to the new agent. New materials of construction had to be tested and fabricated. The speed of response of equipment manufacturers, and particularly of Cyprane Ltd of Keighley, may be related to two factors. The first is that Cyprane, a recently established firm, was anxious to enter the market, and the need for a novel and complex vapouriser gave it the opportunity to do so. Second, technical problems were solved quickly with aid from Mond Division. This may be attributed at least in part to the fact that those originally responsible for synthesising halothane also became responsible, several years later, for testing new materials of construction. Their incentive to see their discovery succeed resulted in extremely active efforts to overcome the subsequent corrosion problems. Without the enthusiastic and fast response of those responsible for designing new equipment, halothane would have spread more slowly.

The second problem was associated with halothane's high cost, and the fact that it was known to be suitable for use in closed-circuit apparatus. These properties made it obviously wasteful to use halothane in open-circuit administration. The anaesthetist who previously had used an open-circuit system to administer ether or chloroform had therefore to alter his technique to use halothane to closed-circuit administration.

Divisibility

One factor that undoubtedly aided halothane's success was the ease with which experiment was possible. This may be attributed to halothane's property of being intrinsically safe when properly administered. This feature, well documented by those who first pioneered halothane anaesthesia, and rapidly published in professional journals, persuaded anaesthetists who might otherwise not have considered themselves well situated to experiment with a new anaesthetic agent that it was safe to do so.

Two further explanations for the easy divisibility of halothane may be advanced. The first is connected with the professional position of the anaesthetist, who could make the decision on which anaesthetic agent to employ without necessarily consulting any other person. His professional independence allowed him to experiment as his own judge-

sion, had to be persuaded of potential advantages before experiment was possible. The second explanation may be equated with the low investment needed for experiment: a bottle of halothane was all that was required before experiment was possible. Although for continued use more accurate (and expensive) vapourisers and closed-circuit equipment were advisable if not mandatory, for experiment alone existing equipment would suffice. This was because during his experimentation the anaesthetist could rely on that best of guides – the condition of the patient – in exercising his judgement as to how to proceed. But exceptional attention is difficult to maintain indefinitely, and improved hardware takes a share of the load. The combination of professional independence and low investment enabled anaesthetists to experiment easily. The experiment demonstrated the advantages that Johnstone had recognised, some of which were hard to convey in written reports. The speed with which halothane has spread owes much to the ease with which experiment has been possible, a factor that is of special importance in a situation where every user has a professional responsibility to satisfy himself as to the propriety of using the new product.

Communicability

We have argued that the ease with which anaesthetists could experiment was an important factor in halothane's success. To persuade anaesthetists of halothane's claim to at least a trial, it was necessary to communicate to them its special features. As has already been seen, its non-explosive nature was the most immediate opportunity of doing this. Yet to persuade anaesthetists to use halothane, its supporters had to demonstrate clear advantages over other anaesthetics. Even when its advantages became apparent, a problem remained, in that some anaesthetists were opposed to halothane because of its cost.

In some ways, their opposition was understandable. Halothane was introduced in the UK at a price of £10.25/250cm³; this compared, as some anaesthetists rapidly pointed out, with a price for chloroform of £0.50/l. The results of halothane's cost were various: as has been seen, anaesthetists who favoured halothane recognised the need to conserve it as much as possible, and hence adopted closed-circuit techniques; others argued that it should be used only for inducing anaesthesia, maintenance being achieved more cheaply with other agents; some senior anaesthetists refused to allow halothane into their departments because of its cost. The comparison between the costs of halothane and chloroform was indeed startling when these costs were measured on a volume basis – and still more so when the anaesthetist drawing the comparison believed the two agents to be similar. Measured against other parameters, however, the cost of using halothane appeared much less daunting: subsequent analysis showed that the cost of all anaesthetic agents (including relaxants, other drugs and soda lime) for operations in which halothane was used was \$4.14 per operation, or \$2.35 per hour of anaesthetic treatment.¹³ In comparison with the large labour costs for surgeon, anaesthetist and nurses this charge was small, and it appeared still less when other possible advantages – reduced blood loss, and hence less need for transfusions, or the quicker induction of patients enabling more operations to be performed in a limited period – were considered. Yet the latter cost comparison was only attractive to those who recognised that halothane produced benefits unobtainable with chloroform,